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NDA: 21-153

Medical Officer's Review

September 21, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-153/ 21-154

MEDICAL REVIEW(S)

SEP 2 1 2000

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	21-153
Sponsor:	AstraZeneca LP (A-Z LP) Wayne, PA
Date Submitted:	December 3, 1999
Drug:	Esomeprazole magnesium (H 199/18; NEXIUM™)
Pharmacological Category:	Gastric Acid Antisecretory; Anti-GERD, Anti-Ulcer; specific inhibitor of the H^+/K^+-ATPase enzyme system
Formulation/Route of Administration	Delayed-Release Capsules for oral administration
Proposed Indications:	a) Healing of Erosive Esophagitis (EE). b) Maintenance of Healing of Erosive Esophagitis c) Treatment of Symptomatic Gastroesophageal Reflux Disease (s-GERD)
Material Submitted/Reviewed:	A total of 359 volumes, including synopsis of application (Item 3, vol. 1, p. 013 through 239), Nonclinical Pharmacology and Toxicology Summary (Item 6), Human Pharmacokinetic and Bioavailability Summary (Item 7), Clinical Summary and Results of Statistical Analyses (Item 8) and Discussion of benefit/Risk Relationship (Item 9).
Reviewer:	Hugo E. Gallo-Torres, M.D., Ph.D. Medical Team Leader

APPEARS THIS WAY
ON ORIGINAL

EXECUTIVE SUMMARY

I. Recommendation

NEXIUM™ (esomeprazole magnesium; H 199/18), the s-enantiomer of omeprazole and the first proton pump inhibitor (PPI) to be developed as a single isomer, is a substituted benzimidazole derivative that suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase enzyme system. Like its parent compound (omeprazole) and other PPIs, NEXIUM blocks the final step of gastric secretion and produces dose-related sustained inhibition of both basal and stimulated gastric acid secretion. Like omeprazole and the other approved PPIs, NEXIUM is of benefit in the three gastroesophageal reflux disease (GERD) related indications that require gastric acid inhibition. These indications are: treatment of erosive esophagitis, maintenance of healing of erosive esophagitis, and treatment of symptomatic GERD. GERD is a chronic recurring and potentially serious, debilitating condition characterized by symptoms of heartburn and regurgitation. Chronic GERD can lead to morbidity ranging from mild esophageal mucosal inflammation to erosions, ulceration, esophageal stricture and, in some patients, transformation to Barrett's esophagus, a premalignant condition. The data presented by the sponsor in NDA 21-153 demonstrate that NEXIUM a) affords rates of healing which are comparable to omeprazole in the treatment of erosive esophagitis; b) is highly effective in the maintenance of healing of erosive esophagitis and c) provides significantly better rates of symptom resolution within 4 weeks than placebo in patients with symptomatic GERD (s-GERD).

The above-described benefits outweigh the potential risks of this drug. Results of pre-clinical evaluations showed that, at equivalent systemic exposure, H 199/18 is pharmacologically and toxicological (including genotoxicity) similar to omeprazole. Like omeprazole, esomeprazole may be administered with adequate safety to humans at the recommended oral doses and treatment duration. Because NEXIUM™ is the s-enantiomer of omeprazole and omeprazole is a PPI that is perceived as safe, NEXIUM is also considered safe. Omeprazole has been marketed worldwide since 1988 and is presently available in 106 countries for various acid-related gastrointestinal disorders. There have been an estimated ——— courses of patient treatments of omeprazole from the time of its introduction into the market through June 30, 1998. This estimate includes all oral formulations of omeprazole. Some patients have received continuous treatment with omeprazole in monitored clinical trials for longer than 13 years [NDA ——— 4 August 1999. General Correspondence, omeprazole ———————— , an extensive clinical experience that confirms that omeprazole is – all things considered safe and well-tolerated. Throughout its development and marketing, certain safety issues have been adequately monitored with omeprazole use and comprehensive updates of these topics have been submitted to the Division. It is concluded that based on the clinical experience with esomeprazole, involving over 5,000 patients and subjects, this drug shares the same overall acceptable safety profile of omeprazole.

The drug is approvable **from a clinical perspective.** No need for risk management actions is anticipated.

There are neither recommended Phase 4 trials nor marketing restrictions. Public outreach or information is not needed.

II. Summary of Clinical Findings

A. Generalities

- NEXIUM™ (identified in clinical trials as H 199/18 and abbreviated in this review as H) is a gastric acid anti-secretory substituted benzimidazole. This compound belongs to the proton pump inhibitor (PPI) class. NEXIUM™ is the s-enantiomer of omeprazole. PPIs exert their activity through inhibition of the H^+/K^+-ATPase enzyme system. This effect abolishes response to all types of gastric acid secretion stimulation, by all gastric messengers (e.g. histamine, gastrin and acetylcholine). NEXIUM™, intended for oral administration, is available as delayed release capsules that bypass the stomach, are absorbed from the intestine and reach the parietal cells via blood, diffusing into the secretory canaliculi. At this site, the (pro)-drug becomes protonated, rearranges to form a sulfenic acid and a sulfenamide and interacts covalently with sulfhydryl groups at critical sites in the extracellular (luminal) domain of the membrane spanning H^+/K^+-ATPase enzyme.
- The pharmacological properties of PPIs make them good candidates for treatment of acid-related disorders. This includes GERD, peptic ulcer disease and Zollinger-Ellison syndrome. Indeed, PRILOSEC (omeprazole, abbreviated in this review as O), the parent compound, has been approved for many conditions including short-term treatment of duodenal ulcer, (also in combination with certain antibiotics to eradicate *H. pylori)*, short-term treatment of gastric ulcer, treatment of erosive esophagitis (EE), treatment of heartburn and other associated symptoms with GERD (s-GERD), maintenance of healing of EE and the long-term treatment of pathological hypersecretory conditions (e.g. Zollinger-Ellison syndrome).
- The PPIs, especially omeprazole, are perceived as very effective and safe drugs and this is reassuring when assessing the merits of the s-enantiomer of omeprazole. Other approved PPIs are PREVACID (lansoprazole), ACIPHEX (rabeprazole) and recently, PROTONIX (pantoprazole).
- The sponsor submitted the following four groups of trials that evaluated the efficacy and safety of NEXIUM in the treatment of the GERD-related indications for which approval is being sought. All of these studies were well-designed and apparently well-executed, double-blind, randomized, with appropriate: a) controls; b) patient populations; c) consistent inclusion criteria and reasons for exclusion; and d) sufficient sample size for appropriate statistical power. Also consistent were the methods to evaluate efficacy and safety and the timing at which these evaluations were carried out. Esophagogastroduodenoscopy (EGD) was assessed by an appropriate grading scale of esophagitis, the LA Classification.

1. There were four controlled clinical trials in healing of erosive esophagitis:
   - 172 [H40 mg (n= — vs H20 mg (n=656) vs O20 mg (n=650)]
   - 173 [H40 mg (n=576) vs O20 mg (n=572)]
   - 174 [H20 mg (n=588) vs O20 mg (n=588)]
   - 222 [H40 mg (n=1,216) vs O20 mg (n=1,209)]

   All four trials were considered pivotal. All four trials used an active comparator, 20 mg of omeprazole (O) once-a-day.

2. There were two controlled clinical trials in maintenance of healing of erosive esophagitis. Both used a negative control (placebo) and were considered pivotal.
   177 [H40 mg (n=92) vs H20 mg (n=98) vs H10 mg (n=91) vs PL (n=77)]
   178 [H40 mg (n=82) vs H20 mg (n=82) vs H10 mg (n=77) vs PL (n=77)]
3. There were five controlled clinical trials in the treatment of s-GERD. Of these, the first two used a negative control (placebo) and were considered pivotal. The other three used a positive control (omeprazole 20 mg once-a-day) and were considered supportive.
   225 [H40 mg (n=123) vs H20 mg (n=121) vs PL (n=124)]
   226 [H40 mg (n=118) vs H20 mg (n=113) vs PL (n=118)]

   SH-QBE-
   -0009 [H40 mg (n=425) vs H20 mg (n=423) vs O20 mg (n=434)]
   -0011 [H40 mg (n=347) vs O20 mg (n=346)]
   -0021 [H20 mg (n=336) vs O20 mg (n=334)]

4. In addition to the above, there was one noncomparative long-term clinical trial, Study 179, which provided supportive information on the effectiveness of H199/18 in the maintenance of healing of EE. Patients who were determined to be EE healed (LA Classification Grade "Not Present") in Study 173 or Study 174 were eligible to receive open-label H199/18 40 mg qd for 12 months as maintenance treatment.
   [808 of the 1,157 patients that completed Study 173 and Study 174 as healed were healed were enrolled in Study 179]

B. Efficacy

- Efficacy was demonstrated for each of the three indications.
- The recommended claims and daily doses are as follows:
  1) Healing of erosive esophagitis
     [20 mg once-a-day for 4 to 8 weeks]
  2) Maintenance of healing of erosive esophagitis
     [20 mg once-a-day for at least 6 months]
  3) Treatment of symptomatic GERD
     [20 mg once-a-day for 4 weeks]

The indicated population is adult patients with GERD. Efficacy in children has not been assessed but it is not expected to be significantly different from that seen with omeprazole, at the same recommended dose regimen (20 mg once-a-day)

- As summarized below, efficacy in **healing of erosive esophagitis** was shown by demonstrating statistical superiority of H40 to O20 in two trials: 172 and 222. However, in Study 173, H40 was not differentiated from O20. Since, in Study 172, H20 was as efficacious as H40 at both 4 and 8 week evaluations, the reviewer's recommended dose for this indication is 20, _____ Moreover, **superiority** of NEXIUM over omeprazole **was not demonstrated** because a) in the two studies where H is shown statistically different to O, the dose of H is **pharmacodynamically thrice** that of the S-isomer in O; b) in spite of this ratio (3:1), H40 was as efficacious as O20 in Study 173;

and c) in Study 174 which used a design that would have shown superiority, if superiority indeed exists, the effects of H20 could not be differentiated from O20. These results indicate that for the healing of erosive esophagitis, H20 is as effective as H40. Although the use of H40 is a good scientific tool to demonstrate that - when compared to the recommended dose of O for this indication (20 mg) - esomeprazole is effective in this indication, a superiority claim of NEXIUM over omeprazole is NOT SUPPORTED by either the comparison of H20 vs O20 or the comparison of H40 vs H20.

Healing of EE
Therapeutic Gain/[p-value]

Study No.	Time of Evaluation (week)	H40 vs H20	H40 vs O20	H20 vs O20
172	W4	4.6% [N.S.]	9.7% [<0.001]	N/A
	W8	3.8% [N.S.]	6.2% [<0.001]	N/A
173	W4	N/A	1.9% [N.S.]	N/A
	W8	N/A	1.2% [N.S.]	N/A
174	W4	N/A	N/A	0.8% [N.S.]
	W8	N/A	N/A	2.3% [N.S.[
222	W4	N/A	12% [0.001]	N/A
	W8	N/A	9% [0.001]	N/A

- Efficacy in **maintenance of healing of EE** was shown in the two placebo-controlled, three-dose-level trials 177 and 178 (see below). In comparison to placebo, all three dose levels of the drug (40, 20 or even 10) are active.

the data show H40 to be superior to H20 in neither of the two trials: in study 177 the therapeutic gain (9.2%) was N.S.; in study 178 the therapeutic gain (0.4%) was also N.S. In addition, because H40 induces significantly higher serum gastrin concentrations

than H20, the reviewer recommends approval of H20 for this indication. For this indication, comparisons to omeprazole are not applicable.

Maintenance of Healing of EE
Therapeutic Gain/[p-value]

Study No.	Time of Evaluation (mo.)	H40 vs PL	H20 vs PL	H10 vs PL	H40 vs H20
177	6	59% [<0.001]	50% [<0.001]	25% [<0.001]	9.2% [N.S.]
178	6	65% [<0.001]	64% [<0.001]	28% [<0.001]	0.4% [N.S.]

- Efficacy in treatment of s-GERD was shown in the two placebo-controlled, two-dose-level trials 225 and 226 (see below). Although both trials showed a lower patient response (complete relief of heartburn) than that seen in EE, this response was well differentiated from placebo. For this indication, as with the previous two, there is no benefit when increasing the H dose from 20 to 40 mg. Thus, the recommended dose of NEXIUM is 20 mg once-a-day. Moreover, claims of superiority to omeprazole are - once again - not supported. Neither H40 (studies -0009 and -0011) nor H20 (Study 021) could be differentiated from O20.

Treatment of s-GERD
Therapeutic Gain/[p-value]

Study No.	Time of Evaluation	H40 vs PL	H20 vs PL	H40 vs H20	H40 vs O20	H20 vs O20
225	W4	20.0% [<0.001]	20.0% [<0.001]	-0.6% [N.S.]	N/A	N/A
226	W4	25.0% [<0.001]	30.0% [<0.001]	-5.0% [N.S.]	N/A	N/A
-0009	W4	N/A	N/A	-3.8% [N.S.]	-1.4% [N.S.]	N/A
0011	W4	N/A	N/A	N/A	2.4% [N.S.]	N/A
021	W4	N/A	N/A	N/A	N/A	2.3% [N.S.]

- As expected of a PPI, the size of treatment effect, especially when compared to placebo, is large and very meaningful clinically. The size of treatment effect in the healing of EE trials is not easily perceived because these are active-active comparator trials. The comparator

(20 mg of omeprazole once-a-day) is very effective in this indication and extremely well differentiated from placebo. This information is described in the package insert for omeprazole. The size of treatment effect in the maintenance of healing of EE is large, a therapeutic gain of at least 50% over placebo in one trial and 64% in the other.

- Finally, the size of treatment effect in s-GERD is good, NEXIUM is reasonably differentiated from placebo in both trials. There is no question that - for this indication – efficacy has been demonstrated. However, NEXIUM (and other PPI, including omeprazole, in other trials) is not very effective in this indication. With 20 mg once-a-day, complete relief of heartburn at Week 4 (Table 54) was seen in only 34% of the patients in one trial and 42% of those in the other. This means that a large proportion of s-GERD patients (66% in one trial and 58% in the other) do not benefit from the administration of this PPI at this daily dose regimen.
- The endpoints studied were reflections of relevant patients benefit and, essentially, attempted to cover all main aspects of GERD. For the healing of EE indication, the effectiveness of the drug was measured by healing of esophageal lesions as verified endoscopically and by symptomatic response [complete relief of heartburn (HB) at the prespecified times (4 and 8 weeks after treatment)]. For the maintenance of healing of EE indication, the effectiveness of the drug was assessed by absence of esophageal lesions upon endoscopy and by lack of appearance of GERD symptoms (HB et al.), both assessed long-term (6 months after randomization to drug or placebo). For the treatment of s-GERD indication, the drug's effectiveness was measured by the clinical endpoint of complete relief of HB at Week 4.
- No comparisons of NEXIUM against H_2-receptor antagonists have been carried out, but PPIs are usually shown to be superior to H_2-blockers. NEXIUM is expected to have similar efficacy and safety to the other PPIs approved for GERD-related indications (omeprazole, lansoprazole, rabeprazole and pantoprazole).
- The reviewer reiterates that, - [redacted] - this s-enantiomer of omeprazole is of similar efficacy to omeprazole.

C. Safety

- Safety testing was adequate. All procedures to gather, assemble, analyze and report adverse events and safety-related matters and follow-up when indicated were adequate. The number of patients exposed per indication and the duration of exposure is summarized in Table 55.
- The key safety population consisted of >4,000 patients for the healing of EE indication, 519 + 807 = 1326 patients for the maintenance of healing indication (these patients were treated for 180 days; the exposed number exceeds the ICH number of 300 to 600 to detect an event with a frequency of ≥0.5%), and 470 + 1530 = 2000 patients for the s-GERD indication.
- Serious side effects were infrequent. For all three indications studied, all serious adverse events (SAEs) were unlikely related to test medication. There is no need for post-marketing monitoring of SAEs.
- The most commonly reported adverse events, per indication, were those related to the G.I. tract plus headache.

	AEs
- Healing of EE	Diarrhea, abdominal pain, nausea, flatulence, and headache
- Maintenance of Healing of EE	Flatulence, "gastritis"
- s-GERD	Diarrhea, G.I. symptoms

In those studies comparing graded dose levels of NEXIUM, there was no dose response. The safety profile seen with H40 and H20 was consistent with that seen with O20.

In the long-term studies of maintenance of healing of EE, the AEs were also predominantly those related to the GI tract.

With the exception of the observed change in serum gastrin concentration, expected of all PPIs, there was no indication that treatment with H199/18 for 4 to 8 weeks in the healing of EE, 4 weeks in the treatment of s-GERD and up to 6 months in the maintenance of healing of EE, results in clinically meaningful effects on laboratory values, systolic or diastolic blood pressure, pulse rate, or body weight.

The long-term consequences of hypergastrinemia are still of some concern. This could still be a risk in certain outliers with risk factors. Since there is a dose-response in the average increases in gastrin levels, and H20 mg is effective, ———————————
The changes in ECL cell evaluations, gastritis ratings, chronic inflammation of the gastric mucosa, atrophy, intestinal metaplasia, and atrophic gastritis are very similar to those seen with omeprazole. This database revealed no evidence of dysplasia or neoplasia but only a few cases of adenomatoid hyperplasia [AH]. These EC-L data seem reassuring. However, little is known about long-term (many years of continuous administration) safety of PPIs.

- With NEXIUM, as with other PPIs, the most frequently reported AEs were either GI symptoms or headache. These manifestations are not related to known animal toxicity. The observed ECL cell hyperplasia with omeprazole is seen in all animal species tested. This finding is likely related to the hypergastrinemia induced by this type of drug.
- Drug-drug interactions are not thought to be a problem with PPIs, NEXIUM included. Listed in the package insert, omeprazole appears to interact with a number of drugs. However, with a few exceptions, identified in the package insert, these drug-drug interactions are not considered to be clinically meaningful.
- The duration of exposure in the pivotal clinical trials was up to 8 weeks in the healing of EE, 4 weeks in the treatment of s-GERD and up to 6 months in the maintenance of healing of EE. However, GERD is a very chronic condition and patients are treated for years with antisecretory medication.

[

- The efficacy/safety ratio is acceptable for the requested duration of exposure.

need for a therapeutic agent capable of providing higher healing rates, and which is as safe and well tolerated as OME. Taken together, these considerations appear to provide an acceptable rationale for testing 40 and 20 mg of ESOME Mg given once-a-day and compare these clinical effects to those seen with OME 20 mg per day.

IV. CRITICAL CLINICAL TRIALS IN NDA 21-153 (TABLE 2)

In support of the approval of ESOME Mg for each of the three indications being sought, the sponsor has presented information from the following 8 critical trials. The main objectives, primary endpoint of efficacy and other experimental features of the design and proposed execution of these critical clinical trials are summarized in Table 2. Included in this Table, under the column labeled REMARKS are the reviewer's initial assessments of the utility of these critical trials in the formulation of the Division's recommendation for regulatory action. The information in Table 2 must be interpreted in conjunction with the data summarized in Section II. of this review (requested labeling).

Indication → **Proposed Dose (mg)** **Proposed Length of Treatment**	**S-T Healing of EE** **40** **4 - 8 Weeks**	**Maintenance of Healing of EE** **40** **up to 12 months**	**Primary Symptomatic GERD** **20** **4 - 8 weeks**
Critical Clinical Trials	No. 172 [H40 vs H20 vs O20] (8 weeks) No. 173 [H40 vs O20] (8 weeks) No. 174[a] [H20 vs O20] (8 weeks) No. 222 [H40 vs O20] (8 weeks)	No. 177 [H40 vs H20 vs H10 vs PL] (6 months) No. 178 [H40 vs H20 vs H10 vs PL] (6 months)	No. 225 [H40 vs H20 vs PL] (4 weeks) No. 226 [H40 vs H20 vs PL] (4 weeks)
Supportive Data		No. 179[b] [H40; no comparator] (12 months)	No. SH-QBE-0008[c] [H40 vs H20 vs O20] (4 weeks) No. SH-QBE-0011[d] [H40 vs O20] (4 weeks) No. SH-QBE-0021[e] [H20 vs O20] (4 weeks)

a) This trial will not be reviewed because it did not test the proposed dose of the drug (40 mg)
b) This trial, where no comparator was used, will be reviewed for safety only
c, d and e) These three trials will not be reviewed because they did not use the same 7-day resolution of heartburn as the critical trials. In addition, study No. SH-QBE-001 did not test the proposed dose of the drug (20 mg).

TABLE 2
NDA 21-153

Main Features of Design and Executon and Initial Assessment of the Utility of the Critical Clinical Trials submitted by the Sponsor in Support of the Approval of the Marketing of ESOME Mg for the Three Indications Sought

Protocol No. County	No. of Patients Enrolled Per Gender	Main Features of the Trial	Groups Being Compared	Remarks
		I. SHORT-TERM HEALING OF EE		
172 (US)	M = 1174 F = 785 Total n = 1960	Randomized, multi-center, double-blind, parallel-group, 3-arm, active controlled Study Population: ca. 1700 patients (560 per arm) with symptomatic endoscopically proven EE Upper G.I. endoscopy at 0, 4 and 8 weeks. The primary endpoint of efficacy was the complete healing of EE (absence of erosions by the Los Angeles classification) induced by H20 or H40 in comparison to O20, each administered q.d. for up to 8 weeks. Secondary questions addressed included whether the same two dose levels of H 199/18 are more efficacious than OME in healing EE at Week 4 and in resolution and relief of symptoms.	All given PO and QD for 8 weeks ESOME Mg (20 mg) [n=656] vs ESOME Mg (40 mg) [n=654] vs OME 20 mg [n=650]	• Useful design • The inclusion of the active comparator (OME at the once-a-day dose of 20 mg, the aproved dose of the drug for this indication) is important to demonstrate that ESOME Mg is efficacious. This comparison does not necessarily prove that ESOME is superior to OME. • Efficacy of the 40 or 20 mg ESOME Mg is shown by demonstrating statistical superiority of each of these ESOME Mg doses over OME 20 mg. • In addition, the large number of patients studied allows dose-response assessments to test the efficacy of the 40 mg in comarison to the 20 mg ESOME Mg dose and choose the best of these two dose levels.
173 (US)	M = 681 F = 467 Total n = 1148	Randomized, multi-center, double-blind, parallel-group, 2-arm, active controlled. Study Population: ca. 1000 (500 per arm) with symptomatic endoscopically proven EE Upper G.I. endoscopy at 0, 4 and 8 weeks Primary and secondary endpoints of efficacy as above.	ESOME Mg (40 mg) [n=576] vs OME (20 mg) [n=572]	• Useful design • This design is aimed at replicating the efficacy of the 40 mg ESOME Mg of showing statistical superiority of this dose of the drug over OME 20 mg, the active comparator being tested at the approved recommended dose.

174 (US)	M = 748 F = 428 Total n = 1176	Randomized, multicenter, double-blind, parallel-group, 2 arm, active controlled	ESOME Mg (20 mg) vs OME (20 mg)	• Not useful design because it did not test the proposed dose of the drug (40 mg). • This trial will not be reviewed. [It showed no difference between H20 and O20]
222 (US)	M = 1482 F = 943 Total n = 2425	Randomized, multi-center, double-blind, parallel-group, 2-arm, active controlled. Study Population: ca. 2425 patients (ca. 1200 per arm) with symptomatic endoscopically proven EE • Study design very similar to that used in Study 172 (see above)	ESOME Mg (40 mg) [n=1,216] vs OME (20 mg) [n=1,209]	• Useful design. • This trial was set to replicate the results in Study 172 (H40 statistically superior to O20) when Study 173 showed no difference between H40 and O20. • The inclusion of the active comparator (OME at the once-a-day dose of 20 mg, the approved dose of the drug for this indication) is important to demonstrate that ESOME is efficacious. This comparison does not necessarily prove that ESOME is superior to OME. • Efficacy of the 40 mg ESOME Mg is shown by demonstrating statistical superiority of this dose of ESOME Mg over the 20 mg dose of OME.
II. MAINTENANCE OF HEALING OF EE				
177 (US)	M = 231 F = 144 Total n = 375	Randomized, multi-center, double-blind, parallel-group, 4-arm, placebo-controlled. Patient Population: Patients with confirmed healing of EE based on endoscopy results at the final visit of Study 172. Of the healed patients in Study 172, 375 were randomized to double-blind treatment in Study 177. Endoscopy at Month 1, Month 3 and Month 6 of treatment. The primary efficacy parameter was the percentage of patients who maintained complete healing of esophageal erosions upon endoscopy evaluation following 6 months of treatment.	All given PO and QD for 6 months ESOME Mg (10 mg) [n=91] vs ESOME Mg (20 mg) [n=98] vs ESOME Mg (40 mg) [n=92] vs Placebo [n=94]	• Both trials used the same very useful design. • The inclusion of the placebo arm is important to demonstrate that ESOME Mg is shown by demonstrating statistical superiority of this dose level over placebo. • Inclusion of three dose levels of the test medication allows a dose-response evaluation thereby permitting a comparison of the effects of low doses (i.e. 10 or 20 mg) vs the highest proposed dose (40 mg) of the drug. (continued on next page)

Similarly, results for investigator-assessed resolution of HB and investigator-assessed resolution of "acid" regurgitation at Week 2 and Week 4 were significantly improved for both the H40 and H20 groups over PL. Results for investigator-assessed resolution of dysphagia for H40 and H20 over PL were not significantly improved at Week 2 nor at Week 4. Although results for investigator-assessed resolution of epigastric pain for H40 and H20 over PL were not significantly improved at Week 2, results for this parameter were significantly improved for H40 and H20 over PL. In Study 226, just as in Study 225, there was no convincing evidence, due primarily to the small number of observations in some cells, that efficacy was different in the following subgroups: gender, age group (<65 y, ≥65 y) and race. Regarding the presence of *H. pylori* at baseline, Study 226 replicated only the findings in the PL group in Study 225: the presence of *H. pylori* appeared to improve the chances of complete resolution of HB at final visit. Results with either H40 or H20 were not replicated. It is therefore concluded that the presence of *H. pylori* at baseline has no consistent predictable effect on the complete resolution of HB at the end of 4 weeks treatment with H 199/18.

The reviewer agrees with the sponsor's conclusion that, in this 4-week study, there were no clinically meaningful differences between the H 199/18 treatment groups and the PL groups in the occurrence of AEs, changes in laboratory values or changes in vital signs. As expected, there were changes (baseline to Week 4) in mean serum gastrin concentration that were higher among patients receiving the PPI than in those receiving PL (mean increase of 100.2, 77.4 and 15.8 pg/ml for the H40, H20 and PL groups, respectively).

In conclusion, the sponsor has submitted results of two studies (225 and 226) demonstrating that NEXIUM (esomeprazole) is effective and safe in the treatment of s-GERD. For both primary and secondary parameters of efficacy H20 is as effective as H40. No increased benefit is achieved by increasing the dose of this PPI from 20 to 40 mg once-a-day.

VIII. INTEGRATED SUMMARY OF EFFICACY

A. Generalities/Questions to be Addressed

Esomeprazole (H199/18 NEXIUM™), the s-enantiomer of omeprazole, is a substituted benzimidazole that suppresses gastric acid secretion by specific inhibition of the action of the enzyme H^+/K^+-ATPase. Like omeprazole and all PPIs, esomeprazole is a prodrug that needs to be activated to exert its antisecretory effects. Omeprazole, approved for a number of indications related to inhibition of gastric acid secretion, is administered at its S and R racemates. The sponsor's approach to assess the efficacy and safety of one of the two isomers in the omeprazole moiety may be clinically important. This is because the use of only one enantiomer of omeprazole may allow separation of efficacy and toxicity. This approach may theoretically lead to a significant increase in therapeutic ratio and a more rational approach in therapeutics. In this instance, the demonstration of a better therapeutic ratio must be eminently clinic because a review of the pharmacologic data demonstrate that optical isomer S does not have a greater affinity than isomer R at the receptor site, is not metabolized at significantly different rates and does not seem to have significantly different affinity for tissue and protein binding sites. It is

worth mentioning that some differences in pharmacodynamic effects may exist between the parent moiety omeprazole and its S-isomer. especially on the first day of administration. But - even if real - it needs to be proven that these differences in PD matter in the healing of EE (evaluated at 8 weeks), the maintenance of healing of EE (assessed at 6 months), and the response to heartburn-associated symptoms in symptomatic GERD (evaluated at 4 weeks). Consequently, any meaningful differences between esomeprazole and omeprazole must be proven in the **clinical arena**. Moreover, any superiority of one compound over the other must be demonstrated at equimolar antisecretory concentrations namely in a weight by weight comparison. This point may be relevant because the S and R isomers possess roughly, the same antisecretory activity. In order to declare the S-form **superior** to omeprazole, these drugs must be tested. at the same amount per day (i.e. 40 H vs 40 O; 20 H vs 20 O). Note that in the comparison H40 vs O20, because of difference in tissue uptake and in particular residence time, the amount of s-isomer in H40 is ca. three times higher than in O20.

In the discussion that follows, the demonstration that 40 H is statistically different from 20 O might demonstrate that the 40 H is **effective** but **not necessarily superior** to omeprazole.

As pointed out in section II of this review, the sponsor's recommended dosage schedules of NEXIUM for the three indications sought are: healing of EE: 40 mg (once daily for 4 to 8 weeks); maintenance of healing of EE: ——— once daily; "clinical trials extended to —— months"); and treatment of s-GERD: 20 mg [once daily for 4 weeks, "if symptoms do not resolve completely after 4 weeks, an additional 4 weeks of treatment should be considered"].

The results of primary efficacy parameter evaluations from the three groups of trials that assessed the efficacy of esomeprazole in the three proposed indications are summarized in Table 54. From each group of trials, those submitted as critical to the specific indication were reviewed in detail. At the end of the review of each trial, the reviewer provided "Additional Comments" with a critique to the adequacy of the design and execution of the trial. In short, all trials depicted in Table 54 were adequately designed (to show what the sponsor set to demonstrate) and apparently well-executed. All in all, the trials had adequate negative (placebo) or positive controls (omeprazole, 20 mg once-a-day), appropriate study populations, consistent inclusion/criteria, sufficient sample sizes for appropriate statistical power and adequate and consistent timing for endoscopic or clinical evaluations. The groups being compared were very similar in demographic and disease baseline characteristics and patients were compliant. It is concluded that the efficacy comparison between the arms of the various trials is valid.

Using the rules of the game specified above and the data displayed in Table 54, the reviewer now attempts to answer the following questions regarding NEXIUM'S efficacy **per each indication**:

1. What studies demonstrate efficacy?
2. Is the reviewer's recommended dose and regimen the same as that recommended by the sponsor?
3. What studies demonstrate that esomeprazole is more efficacious **(clinically superior)** than omeprazole?

B. HEALING OF EROSIVE ESOPHAGITIS

1. For this indication, the question of greater efficacy is not entirely settled. Although study 172 shows statistical difference between H40 and O20 in the proportion of patients healed at 4 and 8 weeks, the therapeutic gain at 8 weeks (6.2%) is of borderline clinical significance. These results (statistical superiority of H40 over O20) are confirmed by those of Study 222. However, in Study 173, H40 could not be differentiated from O20. The conclusion is that, since O20 is known to be active and H40 is not very different from O20, H40 is also active. Activity is also shown for H20 because in two trials (172 and 174) the efficacy of this dose of esomeprazole is similar to O20. In conclusion for this indication: a) both H40 and H20 are active; b) H20 is as active as H40.

2. The reviewer dose not agree with the sponsor's dose recommendation of H40. If a dose of H is to be recommended it would be 20. This is because the only study assessing side by side effects, 172, shows that at Week 8, H20 is as efficacious as H40 (Table 54).

3. There are no studies which demonstrate that H is superior to O, clinically or even statistically. As shown in Table 54, in Study 172, the effects of H20 are not differentiated from those of O20. This conclusion is supported by results in Study 174.

C. MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS

1. For this indication both studies submitted by the sponsor in support of this indication, 177 and 178, provide excellent evidence that esomeprazole is very effective in maintaining reflux esophagitis healed for up to 6 months. Each of the three dose levels of the drug tested (H40, H20, and H10) is shown to be superior to placebo in one trial and these results are replicated in the other.

   In assessing risk to benefit matters related to this indication it is very important to consider **what** is being maintained healed. The answer is in Table 6 (Study 172). The bulk of these patients had LA classification A or B, equivalent to mild to moderate esophagitis. Roughly, 1/5 of the patients had LA classification C (18%) and few (7%) had LA classification D. In this reviewer's opinion, this information argues in favor of maintaining these lesions healed with a lower but definitely efficacious dose of the drug (20 mg once-a-day) rather than 40 mg qd.

[redacted]

2. The reviewer does not agree with the sponsor's dose recommendation of H40. Although study 177 shows some difference between H40 and H20, this difference (9.2%) is: a) not statistically significant and b) of borderline clinical relevance. Furthermore, study 178 shows neither statistical nor clinical difference between these two dose levels of

drug. In addition to being very well differentiated from placebo, both dose levels of H are superior to the lowest dose tested (H10). In summary, it is the reviewer's conclusion that H20 is as efficacious as H40 in maintaining erosive esophagitis healed.

3. The sponsor has presented no results of studies assessing the efficacy of H in comparison to O in the maintenance of healing of EE.

D. TREATMENT OF s-GERD

1. For this indication, the question of efficacy is settled by results of the two pivotal trials, submitted by the sponsor in support of this indication, 225 and 226. These provide unquestionable evidence that esomeprazole is more effective than placebo in the treatment of s-GERD. Each of the two dose levels of drug tested (H40 and H20) is shown to be superior to placebo in one trial and these results are replicated in the other.

Although the therapeutic gains (H > PL) are clinically meaningful (20% in one trial, 30% in the other), the proportion of patients experiencing complete relief of heartburn after 4 weeks of treatment with the drug is low: 34% in trial 225 and 42% in study 226. These proportion of patients experiencing complete relief of HB is considerably lower than the proportion of patients with investigator-recorded complete resolution of heartburn at Week 4 in healing of erosive esophagitis trials: Study 172 (H40=65%; H20=61%): Studies 173 and 222 (H40=68%). The same pattern of response (less symptomatic efficacy for s-GERD than for EE) has been observed with omeprazole and is included in the labeling for this PPI.

2. The reviewer agrees with the sponsor's recommended dose and regimen for this indication since both critical trials demonstrate that there is no added benefit by increasing the dose from 20 to 40 mg once-a-day (Table 54).

3. Results from three clinical trials, -0009, -0011 and -021 (Table 54) clearly show that whether one compares H40 or H20, the effects of esomeprazole in the treatment of s-GERD are **nearly identical** to those seen with O20. **There is clearly no indication that esomeprazole is superior to omeprazole for the treatment of s-GERD.**

E. OVERALL CONCLUSIONS ON EFFICACY

In summary, the overall assessment in NDA 21-153, demonstrate that adequate and well-controlled studies support the efficacy of orally administered esomeprazole in three indications: healing of erosive esophagitis (20 mg once daily for 4 to 8 weeks), maintenance of healing of

baseline and in 44% of those with serum gastrin values of ≥100 pg/ml at baseline. Some of these individual serum gastrin changes appear to be clinically meaningful since they seem to be approaching serum gastrin concentrations found in Zollinger-Ellison syndrome patients.

TABLE 58
Number (Proportion=%) of Patients Experiencing Shifting of Serum Gastrin Concentration (pg/ml) in Uncontrolled, L-T Safety Study 179
H 199/18 40 mg [n=807]

Baseline Serum Gastrin Value	Maximum Post-baseline Result for Serum Gastrin (pg/ml)				
	Missing	<100	100-199	200-299	≥300
Missing	5	15	25	12	10
< 100 pg/ml	14	167 (29.9%)	218 (39.1%)	102 (18.3%)	71 (12.7%)
≥100 pg/ml	3	14 (8.5%)	30 (18.2%)	48 (29.1%)	73 (44.2%)
Depicted are shifts in results between baseline and the maximum post-baseline result.					

NOTE: The above displayed data would argue for the use of doses of NEXIUM lower than 40 mg per day because we do not know the long-term consequences of hypergastrinemia in at least some of the patients administered this PPI at this dose.

X. SUMMARY OF BENEFITS VS RISKS

Esomeprazole is a PPI of proven efficacy for the three indications being sought by the sponsor: short-term healing of erosive esophagitis, maintenance of healing of erosive esophagitis and treatment of s-GERD. Esomeprazole is also safe and well tolerated. Both the efficacy as well as the safety profile of esomeprazole are very similar (and in some instances identical) to omeprazole, a PPI of proven efficacy and safety.

It is important to point out that in order to determine whether one compound is superior to another, these drugs need to be tested at comparable amounts: H20 vs O 20; H40 vs O 40. The sponsor's comparisons of H40 vs O 20 do not yield valid conclusions about the superiority of H over O, although these comparisons are adequate to demonstrate that H is active in the assessed indications. Therefore, the sponsor's conclusion that H 199/18 has been shown to provide a significant clinical advance over omeprazole in the first-line treatment of patients with acid-related disorders is not supported by data.

Specifically, there are no scientific basis for the sponsor's statement that compared to omeprazole, H 199/18 offers a faster and improved resolution of heartburn symptoms and higher rates of healing in the treatment of erosive esophagitis. The two compounds are comparable in

their efficacy for this indication. Like omeprazole, H 199/18 is highly effective in the maintenance of healing of erosive esophagitis but there are no side-by-side studies to assess comparative efficacy of these two drugs in this indication. Although H 199/18 provides predictably and reproducibly higher rates of symptom resolution than placebo within 4 weeks in patients with s-GERD, these effects are very similar if not identical to those seen with omeprazole.

The reviewer agrees with the sponsor's statement that clinical experience in H 199/18, involving >5000 patients and subjects, indicates that this PPI shares the same benign safety profile of omeprazole. This safety and tolerability profile is not unexpected since H 199/18 is the S-enantiomer of omeprazole. These conclusions are supported by comprehensive quantitative and qualitative evaluations of AEs, clinical laboratory findings, vital sign measurements and results of physical examination. In those trials where omeprazole was used as a comparator, the safety profile of the two drugs was similar. However, for both PPIs, distant safety (>20 y continuous administration) as determined by sustained hypergastrinemia and sustained atrophic gastritis in the presence of *H. pylori* infection, is still unsettled.

XI. FINANCIAL DISCLOSURE (21 CFR Part 54)

Financial information was provided for the adequate and well-controlled studies for the requested indications:

	Study Nos.
Healing of EE	172, 173 and 174 (all 3 U.S. studies)
Maintenance of Healing of EE	177 and 178 (all 2 U.S. studies)
Treatment of s-GERD	225 and 226 (U.S. studies) SH-QBE-009, -0011 and -0021 (non-US studies)

These studies, except 225 and 226, were completed prior to 2 February 1999. According to the sponsor, the certification for these studies is subject to the revisions in the requirements for financial disclosure set forth by FDA in the Federal Register and Regulations, 31 December 1998 (volume 63, Number 251), pages 72171 through 72181. Through due diligence, the sponsor determined that there were no disclosable financial interests. Therefore, FDA Form 3454 was provided along with the list of investigators for these studies (sponsor's Attachment A).

Studies 225 and 226 were completed after 2 February 1999. For these trials financial information was collected regarding the financial interests described in 21 CFR § 54.4(a)(3)(i) compensation affected by the outcome of clinical studies, 54.4(a)(3)(ii) significant payments of other sorts, 54.4(a)(3)(iii) proprietary interest in the tested product, and 54.4(a)(3)(iv) significant equity interest in Merck & Co., Inc. or Astra AB. Through due diligence, it was determined that there were no disclosable financial interests for outcome-based compensation, significant payments, or proprietary interests for studies 225 and 226. Therefore, Form FDA 3454 was provided along with the list of investigators for these studies (sponsor's Attachment B).

According to the sponsor, there were eight investigators (two principal and six subinvestigators at seven centers) for Study 225 and six investigators (two principal and four subinvestigators at five centers) for Study 226 who reported significant equity interests. Per 21 CFR § 54.4(a)(3)(v), the steps taken by the study sponsor to minimize any potential bias for these studies were adequate. These steps included: 1) randomization; 2) a double-blind approach; and 3) the fact that both studies were multicenter. An appropriate randomization process precluded any influence the investigator may have on which treatment would be assigned to a given patient. As all treatment assignments were blinded to both investigators and patients, this approach minimized biasing the results in favor of any given treatment. Study 225 included 26 investigational sites, whereas 226 included 27. In addition, in these studies, no center was permitted to randomize more than 24 patients. Form FDA 3455 was provided along with the list of investigators for studies 225 and 226 in sponsor's Attachment C.

XII. RECOMMENDATIONS FOR REGULATORY ACTION

NDA 21-153 for NEXIUM™ (esomeprazole magnesium; H 199/18), the S-enantiomer of omeprazole, submitted for the following three indications, should be approved.

1. **Healing of erosive esophagitis**. The recommended dose is 20 mg once-a-day. Treatment duration should be up to 8 weeks.

   This recommendation is based on results of studies 172, 173, 174, and 222.

2. **Maintenance of healing of erosive esophagitis**. The recommended dose is 20 mg once-a-day. Treatment duration is ——— the randomized clinical trials assessed efficacy at 6 months ———

   This recommendation is based on results of studies 177, 178, and 179.

3. **Treatment of symptomatic gastroesophageal reflux disease**. The recommended dose is 20 mg once-a-day. Treatment duration should be 4 weeks.

   This recommendation is based on results of studies 225 and 226.

In addition, it is recommended not to allow the sponsor to claim that esomeprazole magnesium has any significant clinical advantage over omeprazole in the first-line treatment of these acid-related disorders because no data in support of such a claim have been submitted.

Labeling will be addressed in a separate document.

September 21, 2000

/S/

Hugo E. Gallo-Torres, M.D., Ph.D.

cc:
NDA 21-153
HFD-180
HFD-180/LTalarico S\9-21-00
HFD-180/SAurecchia
HFD-180/HGallo-Torres
HFD-181/MWalsh
HFD-705/Tpermutt
HFD-705/Ytsong
HFD- 40/PStaub
HFD-180/JChoudary
HFD-180/LZhou
r/d 8/7/00 jgw
f/t 9/21/00 jgw
deg: 9/11/00
REVISED 9/15/00

APPEARS THIS WAY
ON ORIGINAL